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## Mental Health and Menopause: Patient-Centric Approaches

### Announcer:

Welcome to CME on ReachMD. This activity entitled "Mental Health and Menopause, Patient-Centric Approaches" was presented during Omnia Education's Women's Health 2022, Beyond the Annual Visit.

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### Dr. Payne:

Hello and welcome. Today we're going to be talking about mental health and menopause, and talking about patient-centric approaches. This talk will be focusing on perimenopause and treating vasomotor symptoms and depression.

I'm Dr. Jennifer Payne. I'm Professor and Vice Chair of Research in the Department of Psychiatry and Neurobehavioral Sciences at the University of Virginia.

These are our learning objectives, identify the patient-centric key factors that contribute to a timely diagnosis of depression during perimenopause and postmenopause, discuss the current guidelines and treatment options for addressing depressive symptoms for patients transitioning into menopause, describe new and emerging therapies and their potential role in reducing menopausal and depressive symptoms, and finally, construct a management strategy that incorporates the individual patient perspective, including how racial, ethnic, and cultural factors influence a woman's menopause experience and preferences for treatment.

This is the overview of the talk for today. First, we're going to talk about definitions. We're going to differentiate perimenopause from menopause. We will then talk about common perimenopausal symptoms, and then focus in on vasomotor symptoms and the treatment of vasomotor symptoms as well as mood symptoms in perimenopausal depression and the treatment of perimenopausal depression.

So what is perimenopause? Perimenopause is the time leading up to menopause. And menopause is actually only one day in a woman's life. And its definition is when a woman has not had a period for 1 year when she's in the appropriate age to experience menopause. The time leading up to menopause is called perimenopause. And it can last years, even as long as a decade. And then once a woman has passed menopause, she is considered to be in the postmenopausal time period.

These are the STRAW staging for reproductive age in women. And I will not go through the details of this slide. But you should know that there are different stages that can be described based on a woman's hormone profile as well as how her menstrual cycle is varying. So you can see that in the reproductive years, there's a regular menstrual cycle. And then when a woman ends - enters into perimenopause, there's an early and late transition to the postmenopausal phase. And during perimenopause, the menstrual cycle becomes irregular, and her hormone levels vary and fluctuate significantly.

These are some statistics from the United States on menopause. So approximately 1.3 million women become menopausal each year. And the age of onset is typically around 51 or 52 years of age. And about 5% of women experience early menopause between the ages of 40 and 45. And another 1% experience premature menopause before the age of 40, due to permanent ovarian failure. So when a woman is in her mid to late 40s and early 50s is the typical time that a woman will be experiencing perimenopause.

So this graph shows you the percentage of women at perimenopause and postmenopause by age, where the darker pink is post menopause and the lighter pink is perimenopause. And you can see that by age 55, a majority, really almost all women have entered into either menopause or perimenopause. In this study, the median age of onset for perimenopause was 47.5 years, and the median age of onset for menopause was 51.3 years.

Now women who are going through perimenopause, which they often refer to as “the change,” have very common physical and physiological symptoms. Physical symptoms are very much characterized by vasomotor symptoms which include hot flashes and night sweats, but on their physical symptoms as well including a reduced sex drive, weight gain, urinary incontinence, vaginal dryness, and bloating.

Along with these physical symptoms, many women experience various mental health symptoms. So they usually complain of increased anger and anxiety, possible depression and depression symptoms. They may also complain of feeling dizzy, having trouble concentrating, more fatigued than usual, and mood swings.

You can see here that this is the number of women that are experiencing various menopausal or perimenopausal symptoms. The most common symptom is interrupted sleep along with hot flashes. Sleep is often interrupted because of hot flashes. So a woman will wake up in the middle of the night usually drenched with sweat, and she may be feeling very hot or extra cold because she's wet. And this obviously can interrupt her sleep. Some women get up, they change their clothes, some women change their sheets, and that can interrupt their sleep. However, women without vasomotor symptoms can have interrupted sleep as well. So many women stopped sleeping well during perimenopause.

The next most common symptoms include a lack of sex drive and mood swings, followed by vaginal dryness and irregular periods.

The vasomotor symptom complex is described here. And what generally happens is that a woman's heart rate increases, her respiratory rate increases, and then she's seized with a sudden sensation of warmth. The flush usually begins in the thorax and neck and then extends outward, to the face and down to the arms. And there's usually profuse sweating in the same area. Many women can perceive the flash before any of the characteristic changes can be measured so they can tell that one is going to be coming on. And they also have nonspecific complaints that result from sleep disruption and interruption including the irritability, the anxiety, nervousness, depression, fatigue, forgetfulness, and inability to concentrate.

Just to speak personally for a moment, I remember when I had my first set of hot flashes at night. I woke up and I could tell I was tachycardic, and that my breath was coming faster than normal. And I thought to myself, ‘Boy, if I was at all prone to anxiety, this would make me feel anxious,’ because it really almost feels like a panic attack. And I think that's where some of the mood and mental health symptoms come from.

Here's the physiological basis for vasomotor symptoms. In menopause, there are few to no responsive follicles in the ovary. And in the absence of the follicles, estrogen levels drop. Lowered and fluctuating estrogen levels impact thermoregulation, and the hypothalamus and pituitary go into overdrive, trying to stimulate the ovaries that don't have any follicles to produce. The gonadotropin pulses intensify, and FSH and LH levels rise. And in neurons in the brain, estrogen loss gives rise to a narrowing of the thermoregulatory zone, and symptoms associated with excursions outside of that zone start to occur. So many women that complain about the hot flashes, but women of this age also have a tendency to get cold more easily because that thermoregulatory zone has shrunk essentially.

So vasomotor symptoms, as I've said, are really the most common symptom associated with perimenopause and menopause. And they occur in about 65 to 79% of women. And 7 to 9% report having at least moderate to severe vasomotor symptoms on a daily basis. And in a quality-of-life study, hot flashes were negatively associated with sleep, concentration, mood, energy, work, and social activities. And so difficulties in all of these areas are associated with the experience of vasomotor symptoms.

This chart shows you the natural history of hot flashes. And what you can see is that hot flashes are most common in early to late perimenopause, and really start to abate by the time a woman enters postmenopause. So only about 16 to 44% of women who are in late postmenopause or have been in menopause for greater than 5 years, experience hot flashes. So the peak is really in that perimenopausal time period.

So some women seek treatment for the symptoms. And there was a population-based survey of women aged 40 to 65. And 60% had sought care for their symptoms. And there are a number of approaches, which we'll get into in a minute, but about 34% reported using hormone therapy, 12% used complementary and alternative medicines and 16% used both. And 38% of women, even though they had sought treatment, remained untreated.

There's some interesting predictors of how long vasomotor symptoms can occur in a woman. So for example, in African American women, the median duration is 10 years, and vasomotor symptoms that start in pre or very early perimenopause last longer. So if a

woman enters perimenopause and immediately starts having vasomotor symptoms, those symptoms are likely to last all the way through perimenopause on into menopause.

There are a number of predictors of long duration. Having a younger age at onset of symptoms, a history of smoking, having a high BMI, worse overall mental health symptoms, and stress all predict a longer period of time having vasomotor symptoms.

For vasomotor symptoms that start after menopause has occurred, the median duration is 3.4 years. So if you make it through perimenopause not having vasomotor symptoms, the likelihood is you'll have a short duration in menopause.

There are a number of predictors of short duration. So being of Japanese or Chinese heritage, being married or partnered, not having financial stress, and more social support, all decrease the duration of vasomotor symptoms. And that tells us that mental health and stress really play a role in these symptoms.

There's an increased economic burden of menopause. And there's a number of comorbidities that really impact on work productivity. So on the left side of the screen, there was a 2005 study of over 4,000 women with menopausal symptoms compared to over 4,000 women without menopausal symptoms. And they found that women with menopausal symptoms had decreased quality of life, increased work impairment, higher healthcare utilization, and many more mental health issues including depression, anxiety, and some medical issues such as joint stiffness.

A 2016 study on women of low socioeconomic status showed patients with menopausal symptoms were more likely to have depression and anxiety, and that it resulted in higher healthcare costs. So over \$7,000 versus under \$6,000, as well as higher healthcare utilization.

So having significant vasomotor symptoms is really a risk for a decreased quality of life and higher health care burdens.

In terms of what this implies for society and work, American employers may experience \$770 in productivity losses per menopausal woman per year. And this is because of higher risks of hypertension, osteoporosis, and depression. And in total, healthcare costs that can be attributed to menopause is nearly \$18 billion annually because of these common comorbidities.

So there's a really huge unmet need here in terms of studying perimenopause and menopause. Clinically, it's understudied. We're still not totally sure what to recommend to women undergoing perimenopause and menopause in terms of their medical and mental health side effects, if you will, of this time of life.

Education about the menopause journey and being a self-advocate is empowering. So where, really as a psychiatrist, I really encourage women to talk about these issues, both amongst themselves, among family, but also with their doctors. And unfortunately, many clinicians lack training and familiarity with patient needs and symptoms. And even when they address these symptoms, they really undertreat. So hormone therapy for hot flashes is not used as much as it probably should be. Antidepressants and non-hormonal medications and behavioral strategies are really underutilized in this population. We also need more research about the pathophysiology and epidemiology across diverse populations and the efficacy of treatments for symptom management.

So in summary, menopausal symptoms and perimenopause affect 1.3 million women per year in the United States. The symptoms are frequent, and often have a major impact on the quality of life, work productivity, health outcomes, and ultimately healthcare costs. Women often do seek treatment, but some do not, even when they should, because they are embarrassed to talk about going through this time of life. And even when women do seek care, they are often undertreated. Unmet needs include more clinical research, better patient education, and perhaps just as important, if not more important, better clinician education on the use of effective treatments and strategies.

There are a number of longer-term health risks associated with menopause. As women age and estrogen levels fall, the risk is increased for genitourinary syndrome of menopause, osteoporosis, cardiovascular disease, and cognitive decline. And currently, we really don't know what the best prevention strategies are yet for these conditions.

So let's dive now into the treatment for hot flashes. First and foremost, women should be educated about avoiding stress, which I'm really not sure how one completely avoids stress these days. But if you can avoid stress, caffeine, alcohol, spicy food, tight clothes, heat, and tobacco, women's symptoms often improve. I always say, you have to avoid all the good things plus stress.

And then there are a number of supplements and medications that some of which have been shown to be helpful and some of which have not been proven to be helpful that can be recommended. And I'll go into detail on these on my future slides. But some of the things that people have used include vitamin B and E, ibuprofen, selective serotonin reuptake inhibitors, and selective norepinephrine and serotonin reuptake inhibitors, gabapentin, clonidine, and hormone replacement therapy. So let's look at some of these.

What are women using? So this was a study of women. And it took a survey of what medications they were using for perimenopausal symptoms, particularly for vasomotor symptoms. And about 36% of women were using a prescription medication, but a number of

women were using other types of over-the-counter or supplement medications, and these included black cohosh, another over-the-counter medication, multivitamins, and calcium supplements. And you can see that the percentage that felt that their medication helped a lot was really in the prescription medication category.

Non-prescription therapies are listed here. These have all been suggested as being good to treat vasomotor symptoms. So this includes black cohosh, dong quai, evening primrose oil, flaxseed, N-3 fatty acids, ginseng, red clover, and vitamin E. However, none have been demonstrated to be better than placebo for vasomotor symptoms. An occasional woman will find a particular supplement helpful. So I don't necessarily discourage the use of these supplements, but just know that none of them have been demonstrated in large numbers to be better than placebo. In addition, it's important to note the black cohosh has been associated with liver toxicity. Rarely, but it can affect someone.

These are prescription medications that have been advocated for vasomotor symptoms which have been effective in reducing vasomotor symptoms. So I've listed here venlafaxine and duloxetine, paroxetine and fluoxetine, but really any of the SSRIs or SNRIs may be effective in reducing vasomotor symptoms. The doses used for vasomotor symptoms are lower than what we'd typically use for depression, and you can get about a 50% reduction in vasomotor symptoms. Gabapentin has also been shown to be effective, again with about a 50% reduction. And clonidine reduces symptoms by about a third.

Here's some clinical pearls about using antidepressants for vasomotor symptoms. The response is usually rapid, usually within even a few days to a week. And if you're purely treating vasomotor symptoms, you're going to want to start with a low dose. And of course, watch for side effects. If you're going to stop the antidepressant, you should taper the woman off of the medication, because there's a discontinuation syndrome for some women when stopping antidepressants. Paroxetine, you should know that you should not prescribe paroxetine in a woman with a history of breast cancer who's taking tamoxifen, because there's a drug interaction. Gabapentin can be used in really low doses like as low as 100 milligrams, but some women require really high doses, as much as 2,400 milligrams. We often prescribe this at night because it's most effective in relieving those night sweats. Again, there's a rapid response, and some women will experience fatigue or dizziness or changes in their mood from gabapentin, so you have to watch for those side effects. Clonidine can be given as a weekly patch in a dosage of 0.1 to 0.3 milligrams, and you want to start low and of course, warn the woman about postural hypotension, and encourage drinking lots of water.

Oxybutynin in dosage of 2.5 to 5 milligrams twice daily can also sometimes be helpful, and it really helps relieve that sweating's part of the vasomotor symptoms. However, there are a number of side effects including dry mouth and difficulty with urinating with this particular medication.

So what about hormone replacement therapy, or what's also been termed menopause hormone therapy with estrogen and progesterone-derived products? So this originally gained popularity in the 1970s and then fell out of favor after the World Health Initiative, or Women's Health Initiative study in 2002, which showed a small increased risk of coronary artery disease, stroke, pulmonary embolism, and invasive breast cancers. However, it's become clearer in recent years that that study had a number of flaws, including women who had already passed menopause in the study sample.

And right now, the North American Menopause Society in 2017 is recommending the following. For women aged younger than 60 years, or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome vasomotor symptoms and for those at elevated risk for bone loss or fracture. MHT is the most effective treatment for vasomotor symptoms of the perimenopausal time period.

In a 2004 Cochrane meta-analysis of 24 randomized controlled trials, found a 75% reduction in weekly hot flashes frequency compared with placebo.

So for women who are not at elevated risk of breast cancer, or stroke, or blood clots, or significant hypertension, hormone replacement therapy can be an appropriate choice for significant vasomotor symptoms that are affecting a woman's quality of life.

The benefits include improvement or even elimination of hot flashes, improved sleep, improved blood flow to the vulva and vagina, and improved sexual function, protection from osteoporosis and fractures, and increase collagen content and skin thickness. The main risks are heart disease, breast cancer, and stroke risk.

There's a new non-hormonal option that is being developed and is currently in clinical trials specifically to target vasomotor symptoms. This is because of KNDy neurons, which include kisspeptin, neurokinin, and dynorphin neurons in the hypothalamus upstream of the ventral hypothalamus. And it's been found that blockage of neurokinin-3 receptors on these neurons, abolishes hot flashes. And so there's a new drug, fezolinetant, that has been shown to reduce the frequency of hot flashes, and as well as a reduction in the VMS score. And I'll show you this data.

The KNDy neurons proliferate when ovaries stop working and stop producing estrogen. And it's been shown that a specific blockade of the NK-3 receptor on KNDy neurons abolishes hot flashes.

This is data that shows that fezolinetant is reducing the frequency as well as reducing the VMS score of moderate to severe vasomotor symptoms. It also reduces the daily total VMS score during week 4 and week 12. This shows that the best dose that reduced the vasomotor symptoms the most was 90 milligrams BID. And you can see that here in the purple column, is high above the rest showing the most reduction and VMS frequency. And you can see that here as well. This is the change from baseline in vasomotor function domain score. And again, that 90 milligrams twice a day had the strongest reduction in vasomotor function domain score.

So targeting of the NK-3 receptor is a highly specific treatment that may address vasomotor symptoms at their origin, and does not involve hormonal manipulation. In early clinical trials, superior efficacy compared to all other non-hormonals and it's highly effective, non-hormonal treatment for hot flashes would be a welcome addition to the clinical armamentarium for menopausal medicine, so stay tuned.

Again, I just wanted to remind you that, although we've been focusing on vasomotor symptoms, really common perimenopausal symptoms include mood symptoms. So anger, anxiety, depression, irritability, and mood swings. So why are women having mood swings during the perimenopause or the menopause transition? Well, essentially, what happens is that the luteal phase - so women often have premenstrual mood symptoms in the luteal phase of the menstrual cycle or right before their period. And in perimenopause, it's almost like those hormonal fluctuations that typically occur in the luteal phase become disjointed from the onset of menses, so that you can go through a significant hormonal fluctuation at times other than the luteal phase in the menstrual cycle. And it's those hormonal fluctuations that really trigger mood swings in susceptible women.

In addition, there are a number of stressors that are specific to this time period. So women who are in their 40s and 50s are often referred to as the sandwich generation. Their children have grown up and are leaving home and are transitioning to adulthood. And at the same time, you know, a woman's parents are getting older and are needing more care. So the leaving of home of children often induces significant sadness and can trigger a depressive episode in susceptible women. But also the stressors of perhaps a career and caring for aging parents can add to symptoms during this time period.

In addition, a lack of sleep and hot flashes can contribute to the development of a depressive episode.

And finally, a woman's body goes a little bit crazy during perimenopause, and many women feel out of control of their body, as well as their mood symptoms. And that can contribute to feeling depressed, angry, and irritable.

There's a domino theory, where the thought is that vasomotor symptoms lead to sleep disturbance, and that not getting enough sleep increases the risk for depression. There are problems with the domino theory because depressive symptoms can precede vasomotor symptoms, and may initially not be accompanied by sleep disturbance. And sleep disturbance is also common in the absence of vasomotor symptoms.

Finally, severe vasomotor symptoms are not always 100% associated with the onset of depressive symptoms. However, nighttime vasomotor symptoms have been linked to depressive symptoms independent of sleep disturbance. And several studies have supported that depressive symptoms are linked with vasomotor symptoms.

So it's important to note that there's likely a, you know, cycle that is all connected, that increases the risk for depressive symptoms. And so even though we don't see a one-to-one connection, these symptoms do appear to be linked and increase the risk for depression.

Here's a chart showing you various risk factors for perimenopausal depression. So demographic factors include being younger age at the time of menopause, so a woman who has menopause in her 40s will be at an increased risk for perimenopausal depression. Being of African American race and having less than a high school education are also risk factors. Having lower socioeconomic support, and stressful life events, and adverse childhood events also increases the risk for depression. Have a pre-existing mood or anxiety disorder prior to perimenopause increases the risk for a period menopausal depression. And also having a history of being sensitive to times of hormonal change. So women who have significant premenstrual symptoms or who had a postpartum depression will be at an elevated risk of perimenopausal depression. In addition, having any chronic medical condition, smoking, and having a higher BMI are risk factors. And then finally, as I mentioned in the last slide, having vasomotor symptoms and sleep disturbance really can increase the risk for depression.

In and women with pre-existing mood disorders, so women with a history of major depression or history with bipolar disorder, perimenopause clearly has an increased risk of developing a major depressive episode. In addition, perimenopause also has an increased risk for new onset major depression. So women who never had a history of depression before.

And it's also important to know that perimenopausal mood instability, so having those quick flashes of anger and irritability that then abates, can be difficult to distinguish from recurrent mood disorders, such as bipolar disorder.

There are a number of lifestyle approaches that can be helpful for women who are having particularly mood symptoms during perimenopause that don't quite meet criteria for an official mood disorder. Exercise absolutely can be very helpful. And again, you want to limit or eliminate alcohol, caffeine, and nicotine. And some women find that changing their diet to a more protein-based diet and eliminating carbohydrates can be helpful. Calcium can also be helpful as well as trying to engage in good sleep hygiene and stress reduction or cognitive behavioral therapy.

So here's my general approach to managing perimenopause in women with and without mood disorders. So in women who are complaining of symptoms, so vasomotor symptoms, and maybe mood irritability, but who do not meet criteria for a mood disorder, I always suggest lifestyle changes first. First of all, we can all afford to be a little bit healthier. And so I think that just makes good clinical sense. I then move to over-the-counter options, so supplements and over-the-counter medications, just because those in general have a lower side effect profile. Then I move to SSRIs or SNRIs, so antidepressant medications. And I'll reserve hormonal options for last. And the reason why I do that, even though we think hormonal options may be superior to antidepressants, is that there are risks with hormonal options. And if we don't need to increase those risks because a woman has a good response to an antidepressant, I think that's better for her in the long run.

And women who do meet criteria for a mood disorder, so either major depression or bipolar disorder, I do use healthy lifestyle changes, but then I move to aggressively treat the mood disorder. So for women with a major depression or bipolar disorder, oftentimes getting their mood disorder in general under control will minimize the perimenopausal mood symptoms as well. You do want to use agents that activate the serotonin system because those can be helpful for vasomotor symptoms as well. And then again, I move on to hormonal options after other options have failed.

So this is another way of looking at this. For women who have evidence of a concurrent mood disorder, you want to move to antidepressants early on. If a woman has no mood symptoms and has medical contraindications to hormone replacement therapy, you can try gabapentin, clonidine, or a low-dose antidepressant. In a woman who has no mood symptoms and no contraindications for hormone replacement therapy and is interested in trying it, hormone replacement therapy is perfectly appropriate. For women who don't have mood symptoms, and no contraindications to hormone replacement therapy but they're not interested in hormone replacement therapy, then one could try alternative treatments that are over the counter.

Here are my key messages. Clinicians need to consistently screen patients for depression and mental health concerns, particularly during perimenopause because they are just so common. Increased clinical vigilance is critical because menopause symptoms overlap with the presentation of depression. And NAMS Guidelines highlight the importance of identifying menopausal stage, assessing co-occurring psychiatric and menopause symptoms, appreciating midlife psychosocial factors, and diagnosing carefully whether a woman has a major depressive episode. Current and emerging therapies may play an important role in managing symptoms of menopause and depression. And clinicians need to consider patient perspective and how cultural factors may influence the menopause experience, treatment-seeking behavior, and preference for treatments.

And I'll stop there. Thank you so much.

**Announcer:**

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